Mail Stop 6010 March 28, 2007

Mr. Stanley N. Lapidus
President and Chief Executive Officer
Helicos BioSciences Corporation
One Kendall Square
Building 700
Cambridge, Massachusetts 02139

Re: Helicos BioSciences Corporation
Registration Statement on Form S-1, filed February 28, 2007
File No. 333-140973

Dear Mr. Lapidus:

We have reviewed your filing and have the following comments. Where indicated, we think you should revise your document in response to these comments. If you disagree, we will consider your explanation as to why our comment is inapplicable or a revision is unnecessary. Please be as detailed as necessary in your explanation. In some of our comments, we may ask you to provide us with supplemental information so we may better understand your disclosure. After reviewing this information, we may or may not raise additional comments.

Please understand that the purpose of our review process is to assist you in your compliance with the applicable disclosure requirements and to enhance the overall disclosure in your filing. We look forward to working with you in these respects. We welcome any questions you may have about our comments or on any other aspect of our review. Feel free to call us at the telephone numbers listed at the end of this letter.

General

1. Please note that our reply to your request for confidential treatment for portions of certain exhibits will be provided under separate cover.

2. Please note that when you file a pre-effective amendment containing pricing-related information, we may have additional comments. As you are likely aware, you must file this amendment prior to circulating the prospectus.

3. Please note that when you file a pre-effective amendment that includes your price range, it must be bone fide. We interpret this to mean that your range may not exceed $2 if you price below $20 and 10% if you price above $20.

4. Please note that where we provide examples to illustrate what we mean by our comments, they are examples and not complete lists. If our comments are applicable to portions of the filing that we have not cited as examples, please make the appropriate changes in accordance with our comments.

5. Please provide us proofs of all graphic, visual or photographic information you will provide in the printed prospectus prior to its use.

6. Please revise your disclosure to identify the publications or research articles in relation to the following statements in the prospectus:

    - In 2003, one of our co-founders, Stephen Quake, DPhil, published the first proof-of-principle demonstration that sequence information could be obtained from single molecules of DNA.

    - In addition, recent research suggests the potential to use our sequencing technology to enable novel studies to characterize regulatory genes and proteins associated with tumor growth.

7. Your make statements about the benefits of your technology but do not explain your basis for these statements. For example, you make the following statements:

    - Our tSMS technology enables the automated, parallel sequencing of billions of individual DNA or RNA molecules at orders of magnitude greater speed and lower cost than the current market-leading sequencing systems.

    - We have designed the HeliScope system to enable substantial throughput and cost improvements in the future without the need for major changes to the technology or replacement of the instrument.

    - Our SimplePrep sample preparation process is cost-effective and can be readily scaled and easily replicated.

    - The HeliScope system is designed to produce a raw throughput approaching one billion bases per hour, representing a 10,000-fold improvement over current market-leading sequencing technologies.

    For each of these statements and other similar statements, please provide disclosure regarding your basis for these claims.

8. The forepart of your prospectus uses jargon and technical terms. For example, these words and phrases appear in the forepart of your prospectus:

- ultra-high-throughput genetic analysis,
- direct sequencing of single molecules of DNA,
- DNA sequencing, gene expression analysis and genotyping, and
- chip- or bead-based arrays or real-time PCR.

Please replace all technical language and jargon with language that can be understood by persons who do not work in your industry. Alternately, if you cannot find substitute language without changing the meaning, prove an explanation of the term where you first use it. See Rule 421(d)(2)(ii) of Regulation C.

9. On pages 1 and 46 you refer to HeliScope as your "first commercial product." On page 3 and in other sections of the prospectus, however, you indicate that you have not yet built a commercial version of your product. Please delete the statement on pages 1 and 46 that HeliScope is a "commericial product" or revise the statement to clarify that you have not yet built a commercial version. Please review the entire prospectus to revise or delete any similar statements.

10. We note the following statements made by your executive officers around March 10, 2007 after the filing of this registration statement at the Advances in Genome Biology and Technology Conference (AGBT) in Marco Island, Florida where the company announced that it had developed novel nucleotide-polymerase formulations that enable the characterization of homopolymers.

    - "This marks an important accomplishment in Helicos' endeavor to deliver a high-performance single molecule sequencing platform," said Stanley N. Lapidus, President and CEO of Helicos BioSciences.
    - J. William Efcavitch, Helicos' Senior Vice President of Product Research and Development, who presented the invention at the AGBT meeting added, "This announcement demonstrates the skill of our innovative and talented team in developing cutting edge technology."

    Please provide us your analysis as to whether these are permitted communications during the offering process.

11. Throughout the prospectus you refer to two significant expectations related to the company's business plan and future viability. One is that the company expects to begin the commercial sale of the product later in 2007 and the other is that the company expects to be able to expand the speed and reduce cost another 100 fold in the next three years. Please advise us as to why these expectations are probable enough to warrant disclosure in the prospectus and provide additional disclosure in the summary and business sections

explaining the basis for these expectations. In this regard, please also clarify what the stages of development are from this point onward toward achieving an additional 100 fold increase in speed and lowering of cost to $1000 and identify the technical difficulties the company has solved to date, the technical difficulties the company must solve before the company can begin commercial sales and the technical difficulties the company must solve in order to increase speed and decrease cost by another 100 fold.

12. Please revise your disclosure in the summary and the business section to better explain your technology in plain English by discussing the constituent parts of your system. For example what does your product incorporate in the way of specific hardware, software, chemicals, biological products, etc. and how do these parts interact when the product is functioning? Which of these constituent parts are proprietary or covered by patents and from which licensors are constituent parts licensed?

13. You explain that one of the advantages of your technology is that will be able to introduce the improvements that will enable the 100 fold change in speed and a reduction in cost without requiring major modifications or introduction of new technology. Please revise your disclosure in the summary and in the business sections to explain the nature of the technology that allows this to happen.

Cover Page

14. Please eliminate the term "sole book-running manager" from the cover page. You can discuss the relationship between the underwriters in the underwriting section if you wish.

Prospectus Summary, page 1

Risks Affecting Us, page 3

15. We note your statement here that you "have limited experience in manufacturing, sales and marketing." It appears, however, that you have no experience in manufacturing, sales and marketing. Please revise this statement accordingly.

Risk Factors, page 8

General

16. Please revise each subheading to ensure it reflects the risk that you discuss in the text. Many of your subheadings currently either merely state a fact about your business, or describe an event that may occur in the future. For example, see the following subheadings.

    - "We will need to develop manufacturing capacity by ourselves or with partners."

- "Our business depends on research and development spending levels of academic, clinical and governmental research institutions and pharmaceutical, biotechnology and agriculture companies."

- "We depend on the assistance of academic collaborators, consultants and scientific advisors to advise us on the development of our technology."

Please succinctly state in your subheadings the risks that result from the facts or uncertainties.

We have not yet built a commercial version of our product. Page 8

17. Please expand your disclosure to briefly describe where your product is in relation to its complete development. For example, is it in the initial phase of development or is it almost complete. To the extent practicable, please also quantify your expected costs to complete the commercial version of your product.

We have a history of operating losses . . . ., page 8

18. Please incorporate into this discussion the rate at which you are currently burning cash on a monthly basis.

19. Please explain why your operating expenses are likely to increase significantly in the near term and quantify the extent of the expected increase to the extent practicable.

We have limited experience in sales and marketing . . . ., page 9

20. To the extent practicable, please revise this risk factor to quantify your expected expenditures as they relate to building your sales force.

If the limited number of suppliers we rely on . . . ., page 11

21. Please identify the suppliers that you substantially rely on for components and materials. Also, to the extent you have any agreements with such parties, please so indicate and describe in your Business section the material terms of the agreements. You should also file the agreements as exhibits to the registration statement. If you have determined that you are not substantially dependent on these parties, please provide us with an analysis supporting this determination and disclose the number of suppliers that you use for components and materials.

Our customers may find replacements for the reagents and supplies that are a part of our instrument systems . . . ., page 13

22. To the extent practicable, please revise this risk factor to quantify what percentage of your revenues you expect to receive from the reagents and supplies that are a part of your instrument systems.

Our products could have unknown defects or errors . . . ., page 15

23. Please disclose your level of product liability insurance coverage. Please also disclose the cost to you of such coverage, if material.

We depend on the assistance of academic collaborators, consultants and scientific advisors . . . ., page 15

24. To the extent that you are substantially dependent on any academic collaborators, consultants and scientific advisors, please name these parties in this risk factor, describe the material terms of your agreements with them in your Business section and file your contracts with them as exhibits to the registration statement. If you are not substantially dependent on any of these parties, please provide us with an analysis supporting this determination and disclose the approximate number of parties performing these services.

We use hazardous chemicals and biological materials . . . ., page 17

25. Please disclose whether you maintain insurance for the use of hazardous materials and, if so, the level of coverage. Please also disclose the cost to you of such coverage, if material.

26. Please discuss if you have been the subject of any investigations in the past.

We depend upon our ability to license technologies. Page 19

27. To the extent that you are substantially dependent on any licensees, please name these parties in this risk factor any describe any specific risks you face as a result of your agreements with them. If you are not substantially dependent on any of these parties, disclose the approximate number of parties performing these services.

You will incur immediate and substantial dilution . . . ., page 23

28. Please revise this risk factor to explain that investors who purchase shares will contribute ___% of the total amount to fund the company but will own only ___% of the shares outstanding.

Use of Proceeds, page 27

29. Please revise the "Use of Proceeds" section to quantify, to the best of your knowledge, the amount of proceeds you anticipate will be used for each of the uses you have enumerated in the section.

Management's Discussion and Analysis of Financial Condition and Results of Operations, page 34

Overview, page 34

30. You state "we have developed a proprietary technology to enable ultra-high-throughput genetic analysis based on direct sequencing of single molecules of DNA or single copies of RNA." However, it appears you have not completed development for "the computational processes necessary for real-time image analysis, base calling and sequence alignment" and "cannot predict the timing or total cost of completion of research and development projects." Please explain these apparent inconsistencies. Expand your disclosure to discuss the elements of your proprietary technology that have been developed and those elements that have not been developed, particularly those affecting commercialization of the HeliScope system. Include the following information relating to your tSMS technology, HeliScope system and commercialization plan.

    - Provide a description of the future applications of the tSMS technology, the related products that you expect to develop and your expected timing for these product introductions. Distinguish between these products and the HeliScope system.
    - You state "after the initial launch of the HeliScope system, we expect to incur significant research and development costs as we develop improvements and future versions of our system." Describe each technology development phase for the HeliScope system, including changes you expect to make to the HeliScope system, and the role expected to be played by the "early adopter customers" in this process.
    - Explain the implications of your development of "computational processes necessary for real-time image analysis, base calling and sequence alignment" to the commercialization of the HeliScope system in 2007. Disclose the amount and timing of the remaining research and development costs that you expect will be necessary to complete development of the HeliScope system.
    - Describe each commercialization phase planned for the HeliScope system. Include a discussion of your expected timing and the amount of costs that you expect to incur in each remaining phase during the commercialization of the HeliScope system.
    - You state "we do not expect to generate significant revenue until at least 2008." Quantify the estimated revenues you expect in 2008 related to the commercialization of the HeliScope system, e.g. revenues generated from sales to the "initial set of early adopter customers."

- You describe development of various subassemblies in the HeliScope system. Explain the extent to which this system is subject to patent protection.
- You refer to a "proprietary" solid state laser illumination module. Describe your basis for deeming this module to be proprietary.
- You refer to "proprietary reagents and supplies." Describe your basis for deeming these reagents and supplies to be proprietary and explain the significance of related sales to your expected future revenue and operating profit.

Financial Overview, page 35

31. Please describe each research and development project and explain how it is relates to your planned commercialization of products, particularly the HeliScope system. Include the following information for each project. Refer to the Division of Corporation Finance "Current Issues and Rulemaking Projects Quarterly Update" under Section VIII – Industry Specific Issues – Accounting and Disclosure by Companies Engaged in Research and Development Activities. You can find it at the following website address: http://www.sec.gov/divisions/corpfin/cfcrq032001.htm.

    - The current status of the project.
    - The costs incurred during each period presented and to date on the project. If you do not maintain any research and development costs by project, disclose that fact and explain why management does not maintain and evaluate research and development costs by project. Provide other quantitative or qualitative disclosure that indicates the amount of the company's resources being used on the project.
    - The nature, timing and estimated costs of the efforts necessary to complete the project, including the anticipated completion date for the project. Disclose the amount or range of estimated costs and timing to complete each phase in the process. To the extent that information is not estimable, disclose those facts and circumstances indicating the uncertainties that preclude you from making a reasonable estimate.
    - The period in which material net cash inflows from the project are expected to commence.
    - The specific risks and uncertainties associated with completing development on schedule and the consequences to operations, financial position and liquidity if the project is not completed as planned.

32. Please describe the nature of start-up manufacturing costs to support your basis for classifying them as research and development expenses.

Liquidity and Capital Resources, page 38

33. On page 34 you state that you anticipate a "significant increase" in your cash outlays during 2007 as you "invest in the necessary commercialization infrastructure such as tooling and

parts inventory for manufacturing and the recruitment of a direct sales and service force." Please quantify the amount of cash you expect to need for these outlays and your sources of funds.

34. An objective of MD&A is to provide information about the quality and potential variability of a company's earnings and cash flow to facilitate investors' determination of the likelihood that past performance is indicative of future performance. This disclosure should discuss and quantify the factors underlying the captions in the financial statements and the impact of known trends and uncertainties. You refer to expected "substantial net losses for the next several years" and to your inability "to estimate the exact amounts of capital outlays and operating expenditures." Also, you indicate that net proceeds from the planned offering, forecasted revenue, cash and equivalents and investment balances will be sufficient to meet your anticipated cash requirements for the next two years. However, you omit quantification of the amounts underlying these disclosures. Please quantify forecasted revenues, expected investments in infrastructure, product development and commercialization and expected net losses. Provide this information on an approximate basis, if exact quantification is not possible.

Contractual obligations, page 40

35. You have entered into license agreements and acquired patent rights that require fixed annual costs and contingent payments upon realization of certain milestones. However, you have omitted related payments from the table of contractual obligations that appear to be directly related to your commercialization plan and thus estimable. Please provide this information in a revised table or provide us your assessment as to why these payments do not meet the criteria of a purchase obligation. If as a result of that assessment you do not include these payments in the table, please include in the liquidity and capital resource section of MD&A, to the extent material, the amount and timing of any commitments that are reasonably likely to be paid. Please refer to Section IV of Financial Reporting Release No. 72.

Critical Accounting Policies and Significant Judgments and Estimates, page 41

36. Your disclosure of critical accounting estimates should provide investors with an understanding of the uncertainties in applying critical accounting estimates and the likelihood that materially different amounts would be reported under different conditions or using different assumptions. It should include quantification of the related variability in operating results that you expect to be reasonably likely to occur. Given your planned product launch in late 2007, we believe that investors would benefit from a discussion of critical accounting estimates that will be necessary as you enter the commercial phase, such as those related to revenue recognition, research and development activities, inventory obsolescence and collectibility of accounts receivable. Please discuss and quantify the expected uncertainties in applying these critical accounting policies and the effect that

reasonably likely changes in the key assumptions underlying these estimates may have on the financial statements. Please refer to Section V of Financial Reporting Release No. 72.

Stock-based compensation, page 41

37. You disclose that "we estimate the volatility of our common stock based on volatility of similar entities." It appears that when you were a non-public company you elected to use the calculated value method for stock option awards to employees and the fair value method for non-employees. If you grant awards to non-employees, it appears that you must use the fair value method for employees, as well. Please explain to us your basis for using the calculated value method for employees, when it appears you use the fair value method for options granted to non-employees. If material, please describe the change in accounting policy that will be required by SFAS 123R in subsequent periods as a public entity and the reasonably likely material future effects. Please refer to the Interpretive Response to Question 4 in SAB Topic 14:B.

38. In order for us to fully understand the fair market valuations of stock-based compensation transactions reflected in your financial statements, please provide an itemized chronological schedule covering all equity instruments issued from January 1, 2006 through the date of your response and provide the following information separately for each equity issuance:

    a. The date of the transaction;

    b. The number of shares issued or options granted;

    c. The exercise price or per share amount paid;

    d. Management's fair market value (or calculated value, if applicable) per share estimate and how the estimate was made;

    e. An explanation of how the fair value of the convertible preferred stock and common stock relate;

    f. The identity of the recipient, indicating if the recipient was a related party;

    g. Nature and terms of concurrent transactions; and,

    h. The amount of any compensation or interest expense element.

    Progressively bridge management's fair market value determinations to the current estimated IPO price range. Reconcile and explain the differences between the mid-point of your estimated offering price range and the fair values included in your analysis.

Provide us with a chronology of events leading to the filing of your IPO, including when discussions began with potential underwriters. If you do not have an estimated offering price in your next filing, we are deferring evaluation of stock-based compensation until your estimated offering price is specified and may have further comment in this regard.

39. You disclose that you retained an independent valuation firm in January 2007 to perform a contemporaneous valuation of your common stock as of January 19, 2007, and to perform two retrospective valuations on your common stock as of March 31, 2006 and October 31, 2006. Please name this independent valuation firm and provide the consent of the firm in the registration statement. Additionally, please provide the disclosures suggested by the AICPA Audit and Accounting Practice – Valuation of Privately-Held-Company Equity Securities Issued as Compensation.

Business, page 46

General

40. Please describe the material terms of your government grant with the National Human Genome Research Institute, including, but not limited to the aggregate amounts, stipulations and term. Please also file any relevant agreements as exhibits.

41. Please also describe the material terms of your collaboration with the Institute for Systems Biology. At a minimum please disclose the following:

    - Each parties obligations, including, but not limited to, research and development funding obligations and obligations to defend patents;
    - Fees paid to date, including upfront payments, annual payments, royalties and milestone payments;
    - Aggregate potential milestone payments;
    - Existence of royalty provisions;
    - Term and termination provisions.

    Please also file any relevant agreements as exhibits. If you believe your collaboration with the Institute for Systems Biology is not a material contract, then provide us with an analysis supporting your determination.

Industry Overview, page 48

42. On page 48 under “Genetic Analysis Market Opportunity and “The Problem”, you discuss the Sanger sequencing method of genetic analysis, particularly regarding its speed. However, there are three types of genetic analysis discussed in the table on page 50. Please explain to us why you use only the Sanger method as a comparison. Please consider revising the disclosure to compare your method to all three methods.

The Helicos Solution, page 51

43. Under "Enhanced Throughput" subsection on page 51, please revise your disclosure to compare your current speed of 90 million bases per hour to the speed of the three genetic analysis methods enumerated in the table on page 50.

44. We refer to your statement that "we believe that the HeliScope system will represent the first genetic analysis platform that can approach the $1,000 Genome goal without requiring major modifications or a new generation of technology." Please disclose the current price level of the HeliScope system and the price level you expect when you begin commercial sales later this year. If the price is substantially higher than $1000 please disclose who you expect will purchase your product.

Intellectual Property, page 60

45. We note that you have included as exhibits license agreements with each of the California Institute of Technology, Roche Diagnostics and Arizona Technology Enterprises. Please describe the material terms of each of these license agreements, including, but not limited to payment provisions, the existence of royalty provisions, aggregate milestones, usage restrictions, exclusivity provisions, obligations/rights to defend, other rights obtained and obligations that must be met to keep the license in place, duration and termination provisions.

Management, page 61

Board of Directors, page 63

46. We refer to your statement on page 64 that each of your directors, other than Mr. Lapidus, qualifies as an "independent director" under the applicable rules of the NASDAQ Global Market and the SEC. We also note that Dr. Afeyan is a co-founder of the company and a 20% stockholder. Please provide us your analysis supporting your conclusion that Dr. Afeyan is an "independent director."

Compensation Discussion and Analysis, page 66

47. Please expand this section to discuss how each compensation element and the company's decisions regarding that element affect decisions regarding other elements. See Item 402(b)(1)(vi) of Regulation S-K.

48. Please expand this section to specifically discuss how corporate performance and individual performance are taken into account in making compensation decisions. You should discuss what specific items of corporate performance are taken into account in making compensation decisions and how specific forms of compensation are structured and

implemented to reflect these items of the company's performance. Further, you should also discuss how specific forms of compensation are structured and implemented to reflect the executive officer's individual performance and/or individual contribution, describing the elements of individual performance and/or contribution that are taken into account. See Item 402(b)(2) of Regulation S-K.

Principal Stockholders, page 81

49. To the extent you have not already done so, please revise to identify the natural persons with investment and voting control over the shares held by each of your 5% stockholder entities.

Exhibits

50. Please include your management incentive bonus plan as an exhibit to the registration statement.

51. We refer to the offer letters that you describe beginning on page 72. These appear to be very similar to employment agreements and should be included as exhibits.

Consolidated Financial Statements

Notes to Consolidated Financial Statements

Note 8. Commitments and Contingencies, page F-16

52. For each of your technology licenses and acquired patents, please disclose and quantify the significant terms of each agreement, including the specific rights that you possess, the degree of usage exclusivity, usage restrictions (if any), contract duration and royalty obligations. Describe the intellectual property associated with each license or patent and how it relates to the development of your tSMS technology.

53. Please disclose and quantify the significant terms governing the following arrangements:
    - Contracts with subassembly manufacturers
    - Contracts related to "research consulting and collaborations"
    - Technical support capabilities
    - Product warranties

Note 10. Redeemable Convertible Preferred Stock, page F-19

54. Please disclose, and explain to us, how you determined the $18.1 million beneficial conversion feature of the Series B Preferred Stock issued in January 2007. Also, tell us your basis under GAAP for adding the $18.1 million beneficial conversion feature to the proceeds of the Series B Preferred Stock issued in January 2007, as disclosed in the pro forma amounts in summary consolidated financial data and the capitalization table.

* * * * *

As appropriate, please amend your filing in response to these comments. You may wish to provide us with marked copies of the amendment to expedite our review. Please furnish a cover letter with your amendment that keys your responses to our comments and provides any requested supplemental information. Detailed cover letters greatly facilitate our review. Please understand that we may have additional comments after reviewing your amendment and responses to our comments.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filings reviewed by the staff to be certain that they have provided all information investors require for an informed decision. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

Notwithstanding our comments, in the event the company requests acceleration of the effective date of the pending registration statement, it should furnish a letter, at the time of such request, acknowledging that:

- should the Commission or the staff, acting pursuant to delegated authority, declare the filing effective, it does not foreclose the Commission from taking any action with respect to the filing;

- the action of the Commission or the staff, acting pursuant to delegated authority, in declaring the filing effective, does not relieve the company from its full responsibility for the adequacy and accuracy of the disclosure in the filing; and

- the company may not assert this action as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

In addition, please be advised that the Division of Enforcement has access to all information you provide to the staff of the Division of Corporation Finance in connection with our review of your filing or in response to our comments on your filing.

We will consider a written request for acceleration of the effective date of the registration statement as a confirmation of the fact that those requesting acceleration are aware of their respective responsibilities under the Securities Act of 1933 and the Securities Exchange Act of 1934 as they relate to the proposed public offering of the securities specified in the above registration statement. We will act on the request and, pursuant to delegated authority, grant acceleration of the effective date.

We direct your attention to Rules 460 and 461 regarding requesting acceleration of a registration statement. Please allow adequate time after the filing of any amendment for further review before submitting a request for acceleration. Please provide this request at least two business days in advance of the requested effective date.

You may contact Frank Wyman at (202) 551-3660 or Don Abbott at (202) 551-3608 if you have questions regarding comments on the financial statements and related matters. Please contact Sonia Barros at (202) 551-3655 or me at (202) 551-3715 with any other questions.

Sincerely,

Jeffrey P. Riedler
Assistant Director

cc: Lawrence S. Wittenberg, Esq.
Edward A. King, Esq.
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53 State Street
Boston, Massachusetts 02109